Diagnosis of HIV-associated tuberculosis

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NO CONFLICTS OF INTEREST TO DECLARE

Lawn & Zumla. Lancet 2011
The Burden of TB in an ART Clinic in Cape Town, South Africa

Burden of TB Among Patients (n=1544) Starting ART in Gugulethu ART Clinic

- All patients
- Past history TB 47%
- Prevalent TB 30%
- Incident TB over 5 yrs 28%

Incident TB During ART

- 40% ‘Unmasking’ of sub-clinical or minimally-symptomatic TB (Lawn et al. AIDS 2009)
- Intensive culture-based screening halves early rate (Lawn et al. AIDS 2010)

TB incidence rate (cases/100pys)

Months ART

Lawn et al AIDS 2006 & AIDS 2009
Prevalent Undiagnosed Sputum Culture-Positive TB at Baseline

Lawn et al AIDS 2009

Prevalence of Culture+ TB on ICF

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>CD4 &lt;100</th>
<th>CD4 &gt;100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lawn et al 2009</td>
<td>25%</td>
<td>38%</td>
<td>16%</td>
</tr>
<tr>
<td>Bassett et al 2010</td>
<td>19%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lawn et al 2011</td>
<td>18%</td>
<td>28%</td>
<td>14%</td>
</tr>
</tbody>
</table>

How to best screen and diagnose??
Symptom Screening

Screen for presence of ≥1 of the following symptoms:
1. Current cough
2. Fever
3. Night sweats
4. Weight loss

Sensitivity: 78.9%
Specificity: 49.6%

Diagnostic Tools

Fluorescence microscopy
Sensitivity 15%-30%

MGIT culture
Time to positivity:
>3 weeks for smear-neg samples
Rationale for ICF in ART Clinics

1. Morbidity
2. Mortality
3. Infection control
4. Prevent MDR-TB outbreaks

Incremental Yield of TB Using Sputum Induction During Screening Pre-ART
Spontaneous Expectoration of Sputum?

- Yes
  - Spot Specimen
  - Induced Specimen

- No
  - Induced Specimen
  - Induced Specimen

Proportion of TB diagnoses (%)

- Induced sputum #2
- Induced sputum #1
- Spot sputum #1

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Patients with symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO screen</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>Any cough</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>Cough &gt;2 weeks</td>
<td>80</td>
<td>60</td>
</tr>
</tbody>
</table>

0 10 20 30 40 50 60 70 80 90 100
Two New Diagnostics

Xpert MTB/RIF  Determine TB-LAM Ag

The NEW ENGLAND JOURNAL of MEDICINE

Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

Catharina C. Boehme, M.D., Pamela Nabeta, M.D., Doris Hilleman, Ph.D., Mark Nicol, Ph.D., Shubhada Shenai, Ph.D., Florella Krapp, M.D., Jenny Allen, B.Tech., Raxim Tahir, M.D., Robert Blakemore, B.S., Rosana Rustomaggi, M.D., Ph.D., Ana Milovic, M.S., Martin Jones, Ph.D., Sean M. O’Brien, Ph.D., David H. Persing, M.D., Ph.D., Sabine Ruesch-Gerdes, M.D., Eduardo Gotuzzo, M.D., Carmina Rodrigues, M.D., David Alland, M.D., and Mark D. Perkins, M.D.
Sensitivity of Xpert MTB/RIF Assay (FIND Multi-Country Evaluation)

Boehme et al NEJM 2010
# Review of Studies

<table>
<thead>
<tr>
<th>Type of TB</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum smear-positive</td>
<td>99-100%</td>
</tr>
<tr>
<td>Sputum smear-negative</td>
<td>57-83%</td>
</tr>
<tr>
<td>Extrapulmonary (range of clinical samples)</td>
<td>53-95%</td>
</tr>
</tbody>
</table>

*Lawn & Nicol. Future Microbiology 2011*

## Limit of Detection of *M. tuberculosis* spiked into sputum

![Graph showing limit of detection of *M. tuberculosis*](image)

131 cfu/mL

*Helb et al. J Clin Micro 2010*
What is the diagnostic accuracy of Xpert MTB/RIF in this most challenging of clinical populations?

Microscopy vs Xpert vs Culture Gold Standard
(All patient samples)

45% increase in case detection
Xpert Sensitivity by Smear Status
(All patient samples)

Xpert Sensitivity: 1 vs 2 samples

1 sputum
2 sputum

All TB
### How to Use in Diagnostic Algorithms??

**Hypothetical cohort (n=1000) with TB prevalence of 20%**

<table>
<thead>
<tr>
<th>Test Combination</th>
<th>Correct TB diagnoses</th>
<th>Missed TB cases</th>
<th>Xpert tests per TB case diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-Screen + microscopy</td>
<td>55.2</td>
<td>144.8</td>
<td>0</td>
</tr>
<tr>
<td>S-Screen + Xpert x1</td>
<td>101</td>
<td>99</td>
<td>6.9</td>
</tr>
<tr>
<td>Xpert x1 for all</td>
<td>120.2</td>
<td>79.8</td>
<td>8.3</td>
</tr>
<tr>
<td>Microscopy + Xpert x1</td>
<td>120.2</td>
<td>79.8</td>
<td>7.8</td>
</tr>
<tr>
<td>S-Screen + Xpert x2</td>
<td>121.2</td>
<td>78.8</td>
<td>11.1</td>
</tr>
<tr>
<td>Xpert x2</td>
<td>146.8</td>
<td>53.2</td>
<td>13.2</td>
</tr>
</tbody>
</table>

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### How to Implement in Screening Algorithms?

**Xpert tests used per TB case diagnosed vs TB prevalence:**

<table>
<thead>
<tr>
<th>Diagnostic algorithm</th>
<th>20%</th>
<th>15%</th>
<th>10%</th>
<th>5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-Screen + Xpert x1</td>
<td>6.9</td>
<td>9.1</td>
<td>13.5</td>
<td>26.9</td>
</tr>
<tr>
<td>Xpert x1 for all</td>
<td>8.3</td>
<td>11.1</td>
<td>16.6</td>
<td>33.2</td>
</tr>
<tr>
<td>Microscopy + Xpert x1</td>
<td>7.8</td>
<td>10.6</td>
<td>16.1</td>
<td>32.7</td>
</tr>
<tr>
<td>S-Screen + Xpert x2</td>
<td>11.1</td>
<td>14.7</td>
<td>22.1</td>
<td>44.4</td>
</tr>
<tr>
<td>Xpert x2</td>
<td>13.2</td>
<td>17.8</td>
<td>26.8</td>
<td>54.1</td>
</tr>
</tbody>
</table>

*Lawn et al PLoS Med 2011*
Xpert MTB/RIF: A ‘game-changer’?

• Pros include
  – Exceptional performance for TB diagnosis
  – Rapid Rrif screening
  – Near patient technology

• Some cons
  – Problems with RIF resistance specificity
  – Expense
    • 4 bay machine $17,000
    • 1 cartridge approx $17
  – Xpert-negative TB
  – Will it be used at point-of-care?

The cost-effectiveness of routine tuberculosis screening with Xpert MTB/RIF prior to initiation of antiretroviral therapy in South Africa: a model-based analysis


Fig. 1. Component costs of care for the first year after screening. Breakdown of the first year of health care costs for an individual initiating ART in South Africa in the Xpert-2-All strategy, a time frame which total costs may be compared for some budgetary purposes. Total per person costs were $3,990. TB: tuberculosis. ARV: antiretroviral.
89 patients had *M. tuberculosis* culture-positive TB

- 1 x Xpert: 58% Xpert-positive + 42% Xpert-negative
- 2 x Xpert: 72% Xpert-positive + 28% Xpert-negative

**Clinical Infectious Diseases 2012**

<table>
<thead>
<tr>
<th></th>
<th>Xpert-NEG (n=25)</th>
<th>Xpert-POS (n=64)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>32.1 (28.3-40.4)</td>
<td>33.5 (26.8-40.7)</td>
<td>0.927</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>16 (64.0)</td>
<td>39 (60.9)</td>
<td>0.789</td>
</tr>
<tr>
<td>BMI</td>
<td>22.1 (20.6-28.5)</td>
<td>21.0 (18.8-23.8)</td>
<td>0.037</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>11.6 (10.4-13.1)</td>
<td>10.1 (8.5-11.7)</td>
<td>0.029</td>
</tr>
<tr>
<td>Neutrophils x10^9 cells/L</td>
<td>2.9 (2.0-3.9)</td>
<td>3.6 (2.5-6.5)</td>
<td>0.021</td>
</tr>
<tr>
<td>CD4 cell count</td>
<td>189 (137-215)</td>
<td>106 (37-185)</td>
<td>0.006</td>
</tr>
<tr>
<td>Viral load (log)</td>
<td>4.4 (4.2-4.7)</td>
<td>5.1 (4.7-5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WHO symptom screen, n (%)</td>
<td>18 (72.0)</td>
<td>55 (85.9)</td>
<td>0.124</td>
</tr>
<tr>
<td>Cough &gt;2 weeks, n (%)</td>
<td>2 (8.0)</td>
<td>20 (31.3)</td>
<td>0.028</td>
</tr>
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Comparison with other TB diagnostics

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<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Smear-positive</td>
<td>0</td>
<td>24 (37.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Culture days to positivity, median (IQR)</td>
<td>21 (17-25)</td>
<td>13.5 (10-18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urine LAM ELISA</td>
<td>2/25 (8.0)</td>
<td>21/59 (35.6)</td>
<td>0.031</td>
</tr>
<tr>
<td>Urine Xpert positive</td>
<td>2/25 (8.0)</td>
<td>15/60 (25.0)</td>
<td>0.084</td>
</tr>
<tr>
<td>Median zones CXR parenchymal abnormal</td>
<td>2 (1-4)</td>
<td>3 (2-5)</td>
<td>0.199</td>
</tr>
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### 90-day ART Programme Outcomes

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<tr>
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<tr>
<td>Alive and in-programme</td>
<td>21 (84.0)</td>
<td>54 (84.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Dead</td>
<td>0</td>
<td>6 (9.4)</td>
<td>&lt;0.179</td>
</tr>
<tr>
<td>LTFU</td>
<td>4 (16.0)</td>
<td>8 (12.5)</td>
<td>0.733</td>
</tr>
<tr>
<td>Transfer-out</td>
<td>0</td>
<td>1 (1.6)</td>
<td>1.0</td>
</tr>
<tr>
<td>Started TB Rx</td>
<td>17 (68)</td>
<td>49 (76.6)</td>
<td>0.4</td>
</tr>
<tr>
<td>Time to TB treatment</td>
<td>32 (26-48)</td>
<td>9 (6-18)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
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### Conclusions

- Xpert diagnoses the ‘more important’ TB cases
- Patients in whom a TB diagnosis is missed (Xpert-negative) have ‘time on their side’ for rescreening
### 90-day ART Programme Outcomes

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<td>9 (6-18)</td>
<td>&lt;0.001</td>
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</table>

**Living with HIV, dying of TB**

We need a POC TB test!
Urine lipoarabinomannan assay for tuberculosis screening prior to ART: diagnostic yield and association with immune reconstitution disease

Stephen D. Lawn\textsuperscript{a,b}, David J. Edwards\textsuperscript{a}, Katharina Kranzer\textsuperscript{a,b}, Monica Vogt\textsuperscript{a}, Linda-Gail Bekker\textsuperscript{a} and Robin Wood\textsuperscript{a}

AIDS 2009
Sensitivity of LAM ELISA for TB Screening Pre-ART

Specificity 100%

Lawn et al. AIDS 2009

Determine TB-LAM Ag

Control band
Patient sample result
Sample pad
Determine TB-LAM Ag

Advantages of Urine Test Strip

- Low-cost ($3.50 per test)
- Truly POC
- Urine easy to obtain and easier / safer / quicker than sputum expectoration or induction
- Hands-on time <5 mins / results in 25 mins
- Simple read-out - no hard-ware
- Rapid diagnosis in those who need quick management decisions
Diagnostic accuracy of a low-cost, urine antigen, point-of-care screening assay for HIV-associated pulmonary tuberculosis before antiretroviral therapy: a descriptive study

Stephen D Lawn, Andrew D Keita, Hopf, Nicole Vogt, Robin Wood

Lancet Infectious Diseases 2011: epub ahead of print

Figure 1: Study profile

- 662 eligible patients enrolled
  - 7 had no urine samples
  - 505 had urine samples
    - 60 had sputum unobtainable
    - 445 had 1039 sputum samples and 435 urine samples
      - 1 had two contaminated culture samples
      - 25 had one contaminated culture sample
      - 18 had no Xpert tests done or they were inconclusive
      - 436 had complete set of LAM ELISA, Determine TB-LAM Ag dipstick, ≥1 microscopy, ≥1 Xpert, and ≥1 culture results
        - 28 each had only one sputum culture result
        - 488 each had two sputum culture results
        - 431 had no tuberculosis diagnosis confirmed by a negative culture result
      - 35 had tuberculosis diagnosis confirmed by ≥1 positive culture
Agreement between two readers?

Overall agreement
514/516
99.6% (95% CI 98.6-100)

Kappa= 0.97
(95%CI, 0.88-0.99)

Agreement between TB-ELISA and Determine TB-LAM Strips?

Overall agreement
507/516
98.3% (95% CI, 96.7-99.2)

Kappa= 0.84
(95%CI, 0.72-0.92)
Sensitivity of LAM POC test

Specificity >98%
all strata

Sensitivity of TB diagnostic assays among all TB patients (n=85)

Liquid culture 100%
Determine TB-LAM 28%
Xpert MTB/RIF 58%
AFB + LAM = 44%
Sputum AFB 28%
### PPV and NPV

<table>
<thead>
<tr>
<th>Patients</th>
<th>TB Prevalence (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>16.5</td>
<td>84.1</td>
<td>89.8</td>
</tr>
<tr>
<td>CD4&lt;50</td>
<td>28.1</td>
<td>92.9</td>
<td>90.0</td>
</tr>
<tr>
<td>CD4&lt;100</td>
<td>22.7</td>
<td>95.0</td>
<td>90.7</td>
</tr>
<tr>
<td>CD4&lt;150</td>
<td>20.5</td>
<td>93.1</td>
<td>90.3</td>
</tr>
<tr>
<td>CD4&lt;200</td>
<td>18.2</td>
<td>88.6</td>
<td>90.3</td>
</tr>
<tr>
<td>CD4≥200</td>
<td>13.2</td>
<td>75.0</td>
<td>89.5</td>
</tr>
<tr>
<td>WHO stage 3/4</td>
<td>22.4</td>
<td>91.7</td>
<td>89.7</td>
</tr>
<tr>
<td>WHO symptom screen positive</td>
<td>19.7</td>
<td>87.2</td>
<td>88.6</td>
</tr>
<tr>
<td>CXR abnormal</td>
<td>26.4</td>
<td>90.3</td>
<td>83.7</td>
</tr>
</tbody>
</table>
Clinical Significance of LAM+ Disease?

• Comparison LAM+ TB cases versus LAM- TB cases
• LAM+
  – More advanced HIV (lower CD4, higher VL)
  – Sicker (lower Hb, BMI, higher neutrophils, more symptoms)
  – Evidence of higher mycobacterial bacillary burden
    (smear+, time to culture positivity, sputum Xpert+, urine Xpert+)

Lawn et al AIDS 2012; submitted

• All 5 deaths within 90 days were LAM+
• i.e. LAM POC TEST DIAGNOSES THE SICKEST PATIENTS WITH HIGHEST MORTALITY RISK
• Use at POC could permit immediate TB Rx and might improve survival
Identifying those with highest mortality risk

**LAM Conclusions**

- Advanced HIV+ with CD4 <150 cells/uL
- Rapid screening + Rx of sickest patients eg pre-ART or new in-patient admissions
- Not a stand-alone test: use in combination
Diagnostic sensitivity of LAM point-of-care assay used alone or in combination with other assays

- Smear
- LAM
- Smear + LAM
- Xpert
- Xpert + LAM

- CD4 >150
- CD4 = 50-150
- CD4 <50

Combinations: advantages

- Smear microscopy + LAM POC
- CXR + LAM POC
- Culture + LAM POC
- Xpert + LAM POC
Overall Conclusions

• Xpert MTB/RIF and Determine TB-LAM Ag both have excellent utility for TB diagnosis among individuals with advanced immunodeficiency

• Sensitivity and specificity aren’t everything:
  – What other information does the test give?
  – Ability to use at point-of-care is a MAJOR issue

• Need for impact studies

Acknowledgments

• Robin Wood, Sophie Brooks, Andrew Kerkhoff, Katharina Kranzer, Monica Yugt, Linda-Gail Bekker, Landon Myer, Francesca Little, Matthew McNally, Pearl Pahlana + staff at Hannan Crusaid clinic

• Mark Nicol, Andrew Whitelaw + NHLS staff

• FIND – preferential pricing of cartridges

• Alere – supplied LAM tests

• WT Bloomsbury Centre